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Enuresis: Causes, Cures and Cautions

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Enuresis is a common benign condition that affects up to 10 percent of school children. Innumerable causes have been proposed: emotional disturbances, small bladders, infections, allergies, polyuria and deep sleep. In an effort to modify abnormal sleep, drugs such as amphetamine or imipramine are frequently prescribed. Imipramine is often very effective but its acute toxicity is not fully appreciated by many patients or their parents. Since accidental imipramine overdose is a serious matter, strict rules regarding its storage and use must be enforced.

ENURESIS is a syndrome characterized by repeated involuntary micturitions after the age of about 5 years. If gross organic causes are evident it is more properly called incontinence. About 60 percent of patients have never experienced a symptom free period and are called *primary* enuretics. When relapse occurs after a long dry period (months or years) the condition is referred to as *acquired* or secondary. The overall course of the condition is benign as noted in the study of Oppel, Harper and Rider of 859 children.[1] In 90 percent of their patients initial dryness was achieved by age 7 and 97 percent were dry by age 12. They also showed that almost half of the bedwetters over age 6 were of the acquired type. The problem is more common among boys but the reported ratio varies widely from series to series.[2]

Causes

Investigations of this condition have generally concerned therapy and the basis upon which groups of test subjects are gathered is usually so unclear that evaluation of cause is difficult. Proposed causes of enuresis can be divided into two groups: somatic and psychogenic. The number of somatic abnormalities that have been proposed are many and can only briefly be touched upon here.

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There is evidence that in some primary enuretics there is reduced functional bladder capacity.[3] It is believed that these children maintain an infantile type of bladder control and, in the absence of voluntary mechanisms, are unable to enlarge their bladder capacity. When this enlargement is induced by consistently forced fluids and training in stopping and starting the stream, improvement often results.

Data have accumulated pointing to an association of sleep abnormalities with enuresis in some patients. Broughton has published an extensive review of the subject[4] and several surveys have shown an apparent connection between "deep sleep" and bed wetting.[5-7] Therapeutic trials using various alerter drugs have substantiated this connection[5,8,9] although drugs such as amphetamine or tricyclic antidepressants have many pharmacological effects unrelated to sleep.

Kjellberg found that over 20 percent of his series of enuretics showed definite evidence of low grade chronic trigonitis or urethritis[10] and others have reported comparable findings.[11] However, it is not generally believed by pediatricians that most primary enuretics have such minor organic problems.

Many parents of enuretics are convinced that in such children more urine than normal is produced. Except for children with sickle cell trait or disease, this has not been shown and Vulliamy's data show that enuresis is not associated with polyuria.[12]

That enuresis results from organic defects in the nervous system has been postulated. Several studies have disclosed a high incidence of electroencephalographic abnormalities in bed wetters as compared with controls[4,13] but such findings are not consistent.[2]

In the past, most pediatricians believed that enuresis was purely a failure of habit formation—inadequate training. While some studies have shown a significantly higher incidence among children of low socioeconomic classes, it would appear that the predisposition to bedwetting transcends family toilet-training techniques.[2] Many children with this problem have emotional disturbances but these are frequently the result rather than the cause of their symptom. There seems to be a good correlation between psychiatric factors and daytime wetting in aquired enuresis but most children with primary enuresis show no emotional causes and the results of psychotherapy are generally disappointing.

There is a remarkable degree of agreement between monozygotic compared with dizygotic twins with regard to enuresis histories.[14] This fact points strongly to a genetic basis for the disorder.

A number of physicians have proposed allergy as the cause of some cases of enuresis. They believe that various foods or chemicals can produce low grade bladder irritation with resultant urgency. No controlled studies have substantiated these findings.[15]

Cures

At present, treatment is often based upon the prejudices of the therapist. For those who accept the evidence that bed wetters maintain an infantile bladder control and are, consequently, unable to enlarge bladder capacity in a normal fashion, forcing of fluids during the day plus "bladder stretching" techniques are employed. In a cooperative child, results are often quite good after the child is able to hold 300 ml or more. There are no side effects.[3]

Physicians and parents inclined toward habit modification report excellent results using various pavlovian conditioning devices through which a few drops of urine close an electrical circuit and activate a bell or buzzer awakening the child automatically.[16] Again, this method is relatively safe although, if the alarm fails to awaken the child (a common situation), direct current from the apparatus travels through the adjacent skin and can produce indolent ulcers.[17]

Cholinergic blocking agents have been used for decades as primary or adjunctive therapy. Propantheline (ProBanthine®) is ineffective when given alone and the same is true for atropine and other belladonna mixtures.

The amphetamines have been employed with considerable success in some patients.[5,6,19] Reports of bedtime doses of d-amphetamine as high as 15 to 20 mg after which the child stays dry and yet sleeps are not uncommon. Such instances are emphasized by the "deep sleep" advocates as proof of their theory. As dosage increases insomnia eventually intervenes initiating a drop in dose. Mild nervousness is occasionally a problem but no serious toxicity usually occurs.[20]

Imipramine (Tofranil®) is effective in the treatment of some children with enuresis and its use has supplanted amphetamine. Many investigations over the past 15 years attest to this and several such studies were well controlled.[9,18] The drug is usually given a few hours before bedtime and the recommended dose is 25 to 50 mg in children from 6 to 12 years and as high as 75 mg in older patients. Most studies relating to efficacy do not clearly describe diagnostic criteria but it would seem that *primary* enuresis shows the greatest improvement with imipramine. After dryness is achieved, slow withdrawal of the drug is frequently followed by recurrences leading to repeated courses of therapy. This confronts the physician with a dilemma since the safety of long-term use of the drug in children has not been established.

Subacute toxicity of imipramine includes nervousness, insomnia, weight loss, syncope and vague gastroenteric complaints when using recommended doses. At these doses, cardiac toxicity is very rare in otherwise normal children[21] but this is not true for adults. Vague withdrawal symptoms have been reported.

Accidental or intentional acute overdosage is a very serious matter and represents a medical emergency.[22-24] Major symptoms occur after total acute doses of 10 mg per kg of body weight and include: convulsions, shock, coma, tachycardia, fever and cardiac arrhythmias including ventricular fibrillation (and death). Management of these situations is often difficult and imipramine is *not* dializable.[25,26]

Recently, Goel and Shanks reported their experience with 60 children poisoned with tricyclic antidepressants (imipramine or amitriptyline). Of these cases, 34 represented ingestion of drug

prescribed for enuresis, either for the patient himself or for a sibling.[22] These investigators commented that most of the parents regarded bed wetting as trivial and, consequently, the medicines prescribed for it as harmless. The authors raised the important question of whether the risks resulting from the broad availability of these compounds outweighed their benefits for bed wetters. Mofenson, Greensher and Horowitz[27] brought up the same question in 1972 as did Parkin and Fraser.[24] Fortunately, improved methods of treatment of imipramine overdose with intravenously given physostigmine are usually effective. Such treatment, as described by Rumack,[29] includes an initial therapeutic trial of 0.5 mg of physostigmine salicylate administered slowly intravenously. If signs of imipramine toxicity persist and no cholinergic effects are induced, the antidote can be readministered at five minute intervals up to a maximum total dose of 2 mg (up to 4 mg in adults). Physicians should not use intravenously administered physostigmine without being familiar with its undesirable effects and its contraindications.

Cautions

As long as imipramine is commercially available, it would seem that the following recommendations are reasonable concerning the treatment of enuresis.

- Prescribe imipramine only for children whose families understand that it is a dangerous drug and who will monitor its administration and storage with the same care as with digitalis or morphine.
- If the family is disorganized or unreliable, then imipramine should *not* be prescribed.
- When prescribed, imipramine should be dispensed in child-proof containers and should be locked up, and each prescription should be written for a small number of tablets.
- A 30-ml bottle of ipecac syrup (with instructions for use) should be in every home in which imipramine is stored.
- Strong consideration for nondrug regimens should be made for initial therapy of all bed wetters[28] in view of the benign natural history of the condition.[1]

It would also seem desirable that the manufacturer of imipramine modify its advertising literature and sales methods so that the above noted benefit to risk considerations are presented in a balanced fashion. Finally, it is urged that physicians in the United States report *all* treated cases of imipramine poisoning to the National Clearinghouse for Poison Control Centers (DHEW-FDA), regardless of the purpose of the original prescription, so that sound incidence and clinical toxicity data will be available to help monitor compliance with the above recommendations and to aid in formulating improved treatment recommendations.

Trade and Generic Names of Drugs

Dexedrine® ..... d-amphetamine sulfate
Tofranil® ..... imipramine hydrochloride
Elavil® ..... amitriptyline hydrochloride
Antilirium® ..... physostigmine salicylate

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